Remarks

Status of the Application

- Claims 2 – 9 are rejected under 35 USC 112, for lacking enablement for preventing tinnitus.
- Claims 1 and 4 – 9 are rejected under 35 USC 112, for lacking enablement for treating with any NMDA receptor agonist.
- Claims 1 – 9 are rejected for being obvious over Tabuchi, et al., in view of Donovan.

Claims 2 – 9 are Rejected under 35 USC 112 for Lack of Enablement

Examiner has rejected Claims 2 – 9 for lacking enablement. Specifically, the Examiner states: "... the specification, while being enabling for the "treatment of tinnitus" does not reasonably provide enablement for the "preventing tinnitus"." Pending Action, page 2. However, and without necessarily conceding to the merits of Examiner's argument, Applicants have canceled Claim 2, which is directed towards the prevention of tinnitus, and amended the appropriate dependant claims (3 – 6) so that the no longer depend from canceled Claim 2. Applicants respectfully submit that the rejection is now moot and request the withdrawal of the rejection.

Claims 1 and 4 – 9 are Rejected under 35 USC 112 for Lack of Enablement

Examiner has rejected Claims 1 and 4 – 9 for lacking enablement. Specifically, Examiner states "... the specification, while being enabling for the treatment of tinnitus administering **specific receptor antagonist** ... does not provide enablement for the term "**an NMDA receptor antagonist**"." Pending Action, page 6, emphasis in original.

However, and without necessarily conceding to the merits of Examiner's argument, Applicants have folded the limitation of Claim 3 (*i.e.*, treatment with ketamine) into Claim 1 and canceled Claim 3. Applicants respectfully submit that the rejection is now moot and request the withdrawal of the rejection.

Applicants also respectfully remind Examiner that ketamine was selected in response to a species requirement and that upon allowance of the claims directed towards ketamine, the additional NMDA receptor antagonists 7-chlorokynurenate, D-AP5, MK 801 and gacyclidine listed in Claim 5 of the original claim set should be considered for allowance.

Claims 1 – 9 are Rejected under 35 USC 193(a) as Obvious

Examiner has rejected Claims 1 – 9 as being unpatentable over Tabuchi, et al., in view of Donovan. Applicants respectfully traverse this rejection.

Examiner states:

> It would have been obvious to one of ordinary skill in the art to employ ketamine for the treatment of tinnitus induced by cochlear excitotoxicity provoked by ischemia because Tabuchi, et al., teach the protective effect of ketamine in cochlear injury/dysfunction due to ischemic-reperfusion and because tinnitus is a disorder of cochlear as taught by Donovan. Pending Action, page 9.

Applicants respectfully submit that Tabuchi, et al., teaches "ketamine and dextromethorphan ameliorated of the postischemic CAP [compound action potential] threshold shift." Tabuchi, et al., page 48, column 1, first full paragraph. Furthermore, Applicants agree with Examiner that Tabuchi, et al., do not teach that the compounds used in their studies (i.e., ketamine, dextromethorphan and MK-801) are effective in the treatment of tinnitus. ("Tabuchi, et al., do not expressly teach the treatment of tinnitus ..." Pending Action, page 8).

The presently claimed invention is limited to the treatment of tinnitus "induced by excitotoxicity" and wherein treatment "suppress[es] or reduce[s] NMDA receptor mediated aberrant activity of the auditory nerve." Excitotoxicity is defined in the art as the pathological process by which nerve cells are damaged and killed by glutamate and similar substances. (www.wikipedia.org/wiki/Excitotoxicity; pending specification paragraph [0012]). NMDA antagonists block receptor binding of glutamate and similar substances thereby suppressing or reducing NMDA receptor mediated aberrant activity of the auditory nerve. Pending specification, paragraph [0024].

Tabuchi, et al., do not teach that the ischemic/reperfusion model that they used caused damage to nerve cells by excitotoxicity or that the NMDA antagonists used in their work exerted their effect by blocking NMDA receptors. Rather, Tabuchi, et al., teach against the present invention by teaching that ketamine is effective in their system by working via a pathway(s) other than NMDA-receptor inhibition. Tabuchi, et al., state:

> "Since MK-801, the most potent NMDA antagonist among the three agents examined in the present study, failed to attenuate the postischemic threshold shifts, we concluded that NMDA antagonists do not have any protective effect on cochlear ischemia-reperfusion injury ..." Tabuchi, et al., page 48, column 1, first full paragraph.

and,

> "In contrast to the negative effect of MK-801, ketamine and dextromethorphan ameliorated the postischemic CAP threshold shift. It is highly likely that these agents act via a pathway(s) other than NMDA-receptor inhibition." Tabuchi, et al., page 48, column 1, first full paragraph, emphasis added.

and,

> "... the protective effects observed in the present study [by ketamine and dextromethorphan] may be explained, at least in part, by the involvement of ... [the] blockade of nitric oxide release and increase in dopamine release caused by ketamine." Tabuchi, et al., page 48, column 2, first paragraph.

It is of importance to note that the most potent NMDA antagonist tried by Tabuchi, et al., MK-801, did not show any protective effect. Tabuchi, et al., abstract. In view of these statements by Tabuchi, et al., Applicants submit that the teachings of Tabuchi, et al., are not applicable to the present invention of treating tinnitus *induced by cochlear excitotoxicity* which requires suppression or reduction of *NMDA receptor mediated aberrant activity of the auditory nerve*, as claimed. Thus, Tabuchi, et al., do not teach that ketamine can be used for the treatment of disease states induced by cochlear excitotoxicity and treated by NMDA-receptor inhibition, as presently claimed.

Donovan does not supply the claim elements missing from Tabuchi, et al., and, therefore, Tabuchi, et al., in view of Donovan cannot teach or fairly suggest the present invention as amended. Furthermore, Donovan does not provide an unambiguous relation to the disorder "tinnitus" since only a small portion of animals suffering from hypoxia ischemia model as used by Donovan also exhibit tinnitus. In contrast, in order to test their theory that NMDA antagonists would provide relief for tinnitus, Applicants found it necessary to develop an animal model suitable for this use since prior art animal models were unsuitable (*see*, Exemplification section of specification).

Further still, the tinnitus model used by Donovan represented "a particular form of inner ear tinnitus ... which is due to functional disturbances of the synapse between cochlear hair cells and afferent dendrites of the auditory nerve." Donovan, column 2, past paragraph. In contrast, Applicants found that with their model system,

> "Overall, these results suggest that hair cell loss induced by acoustic trauma does not play a significant role in the generation of tinnitus [in Applicant's model system], and point to cochlear excitotoxicity as the mechanism at its base." Pending specification, paragraph [0062].

Thus, the model system used by Donovan was not adapted for use in determining the validity of treatments for tinnitus induced by cochlear excitotoxicity and treatment by NMDA-receptor

inhibition, as presently claimed. Applicants submit that for the reason given above, Tabuchi, et al., in view of Donovan does not teach or fairly suggest the presently claimed invention.

In view of the forgoing, Applicants respectfully request the withdrawal of the rejection and the issuance of the pending claims.

Summary

Applicants respectfully request consideration of the pending specification in view of this Response. Any deficiency or overpayment should be charged or credited to Deposit Account No. 50-4514.

Respectfully submitted,

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